

Global and Epigenome-wide DNA methylation profiles and exposure to ambient air pollution

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Air pollution and DNA methylation

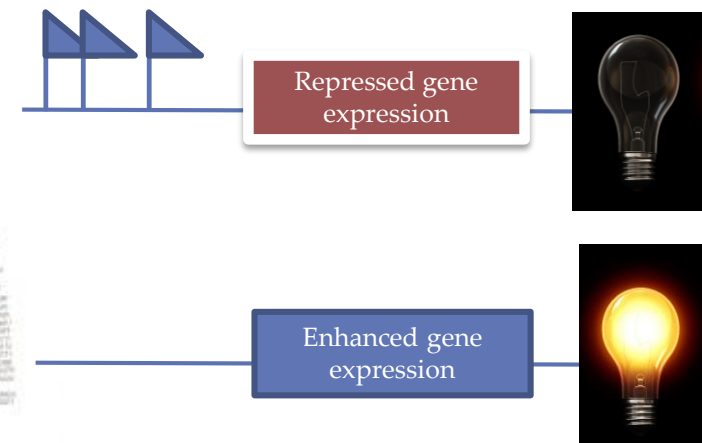
- **Global hypomethylation** has been associated with increased air pollution before:

- Different exposures: black carbon, PM_{2.5}, SO₂, NO₂, PAHs
- Adult / prenatal exposure
- Different techniques: LINE, tandem repeats, LUMA, ELISA, ...

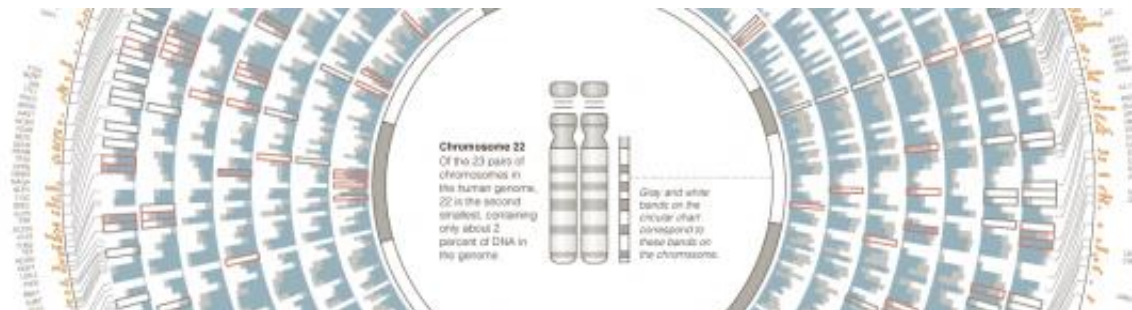


- **Gene specific methylation**

- Inflammation and immunity genes
- TET methylation

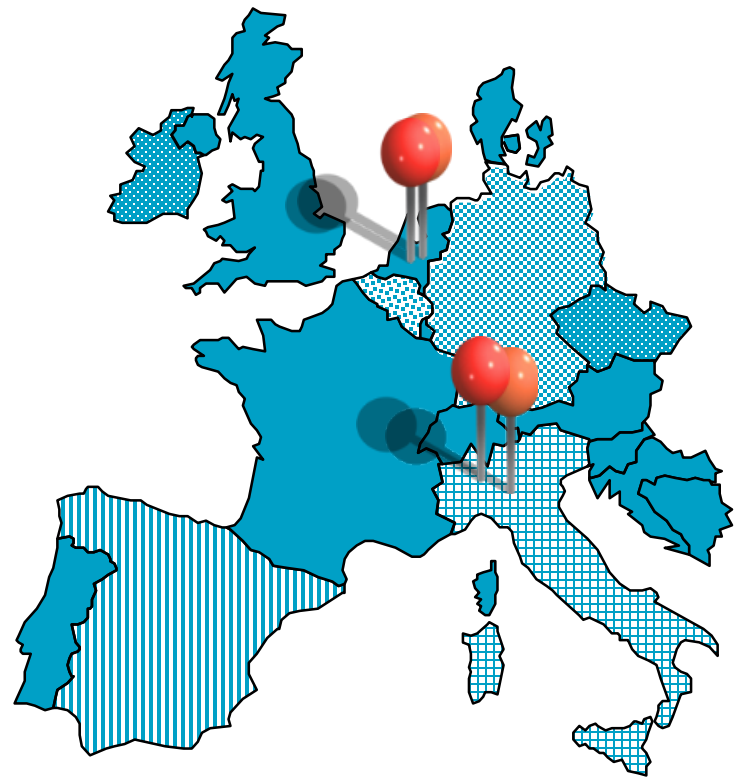


No epigenome wide study for long term exposure



Methods

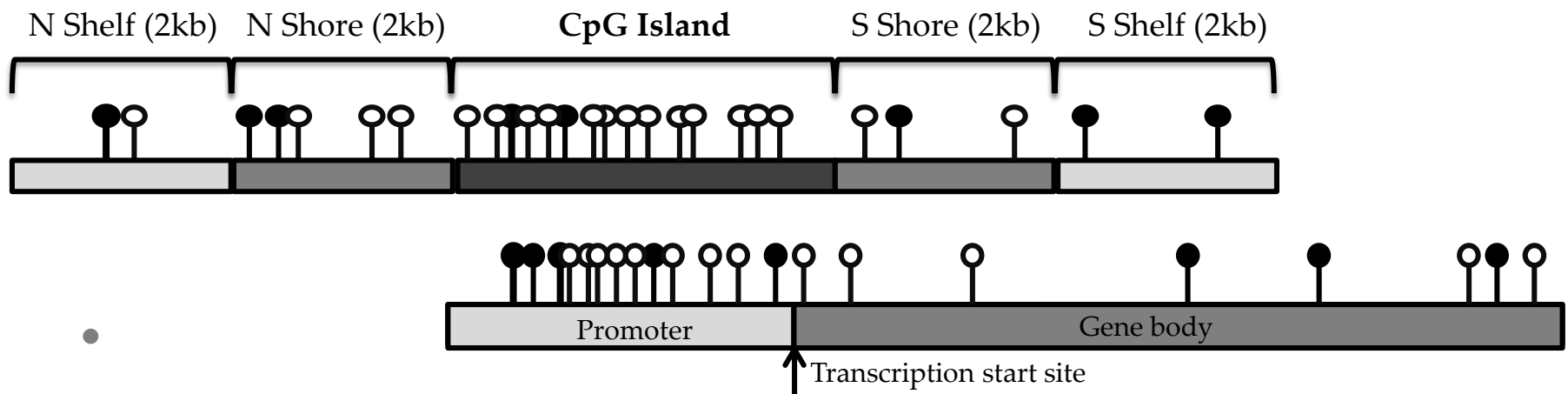
- Illumina Infinium 450k Human Methylation Assay
- Discovery
 - EPIC-Italy
 - EPIC-NL
- Beta-values $\beta = \frac{M}{U + M}$
- Beta-regression adjusted for
 - Position on the array, gender, age, smoking, case status, WBC*
 - Bonferroni correction
- Air pollution data
 - Land Use Regression models in ESCAPE
 - NO₂, NO_x, PM_{2.5}, PM_{coarse}, PM₁₀, PM_{2.5} absorbance



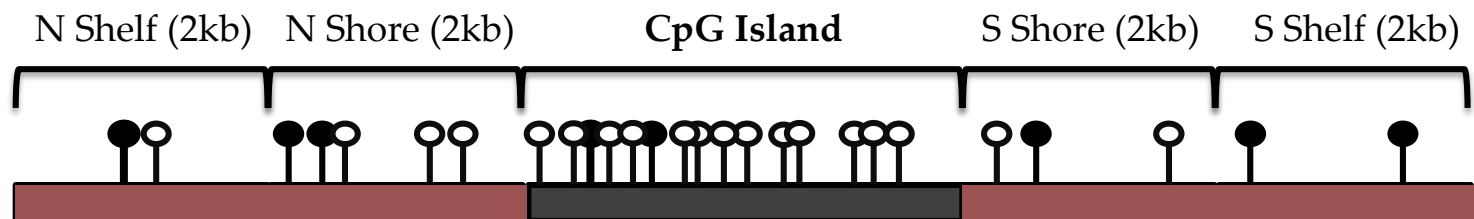
Does air pollution cause a change in global DNA methylation?

- Mean beta-value over all probes
- Probes were categorized into different classes according to their physical and functional location

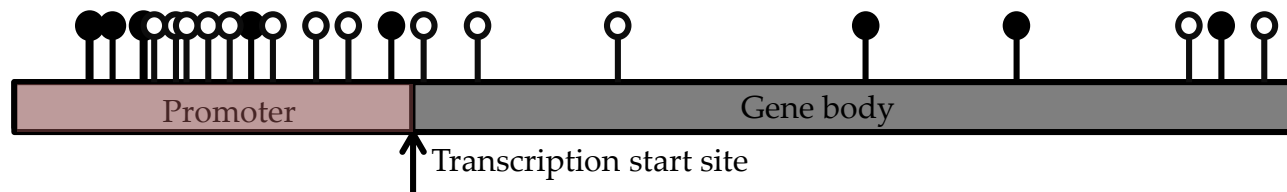
	Mean (sd)
Chromosomes	
1-22	0.53 (0.006)
XY	0.54 (0.054)
Relation to CGI	
Shelf	0.77 (0.008)
Shore	0.49 (0.006)
Island	0.24 (0.007)
Functional region	
Transcription start site -1500	0.40 (0.006)
Transcription start site - 200	0.21 (0.007)
5' UTR	0.40 (0.006)
1 st Exon	0.26 (0.007)
Gene body	0.66 (0.006)
3' UTR	0.76 (0.008)



EPIC-Italy			EPIC-NL	
	$\beta \pm SE$	p-value	$\beta \pm SE$	p-value
NO₂				
Somatic probes	-1.98e-4 \pm 5.74e-5	0.0005	-2.11e-3 \pm 1.16e-3	0.07
Relation to CpG island				
Island	-7.37e-5 \pm 5.53e-5	0.18	-1.47e-3 \pm 1.27e-3	0.25
Shelves	-4.22e-4 \pm 1.16e-4	0.0003	-4.23e-3 \pm 2.08e-3	0.0419
Shores	-2.21e-4 \pm 6.16e-5	0.0003	-2.34e-3 \pm 1.10e-3	0.0339
Position on Gene				
Promoter	-1.60e-4 \pm 5.10e-5	0.0017	-1.82e-3 \pm 1.06e-3	0.09
Gene body	-2.15e-4 \pm 5.93e-5	0.0003	-2.20e-3 \pm 1.12e-3	0.05
Intergenic	-2.60e-4 \pm 7.45e-5	0.0005	-2.52e-3 \pm 1.40e-3	0.07
NO_x				
Somatic probes	-6.77e-5 \pm 2.65e-5	0.0107	-6.09e-4 \pm 4.93e-4	0.21
Relation to CpG island				
Island	-3.46e-5 \pm 2.57e-5	0.18	-5.23e-4 \pm 5.39e-4	0.33
Shelves	-1.30e-4 \pm 5.34e-5	0.0149	-1.74e-3 \pm 8.78e-4	0.0474
Shores	-7.33e-5 \pm 2.86e-5	0.0104	-1.10e-3 \pm 4.66e-4	0.0188
Position on Gene				
Promoter	-5.84e-5 \pm 2.36e-5	0.0134	-5.46e-4 \pm 4.54e-4	0.23
Gene body	-7.11e-5 \pm 2.74e-5	0.0094	-7.36e-4 \pm 4.78e-4	0.12
Intergenic	-8.1e-5 \pm 3.45e-5	0.0187	-8.13e-4 \pm 5.95e-4	0.17

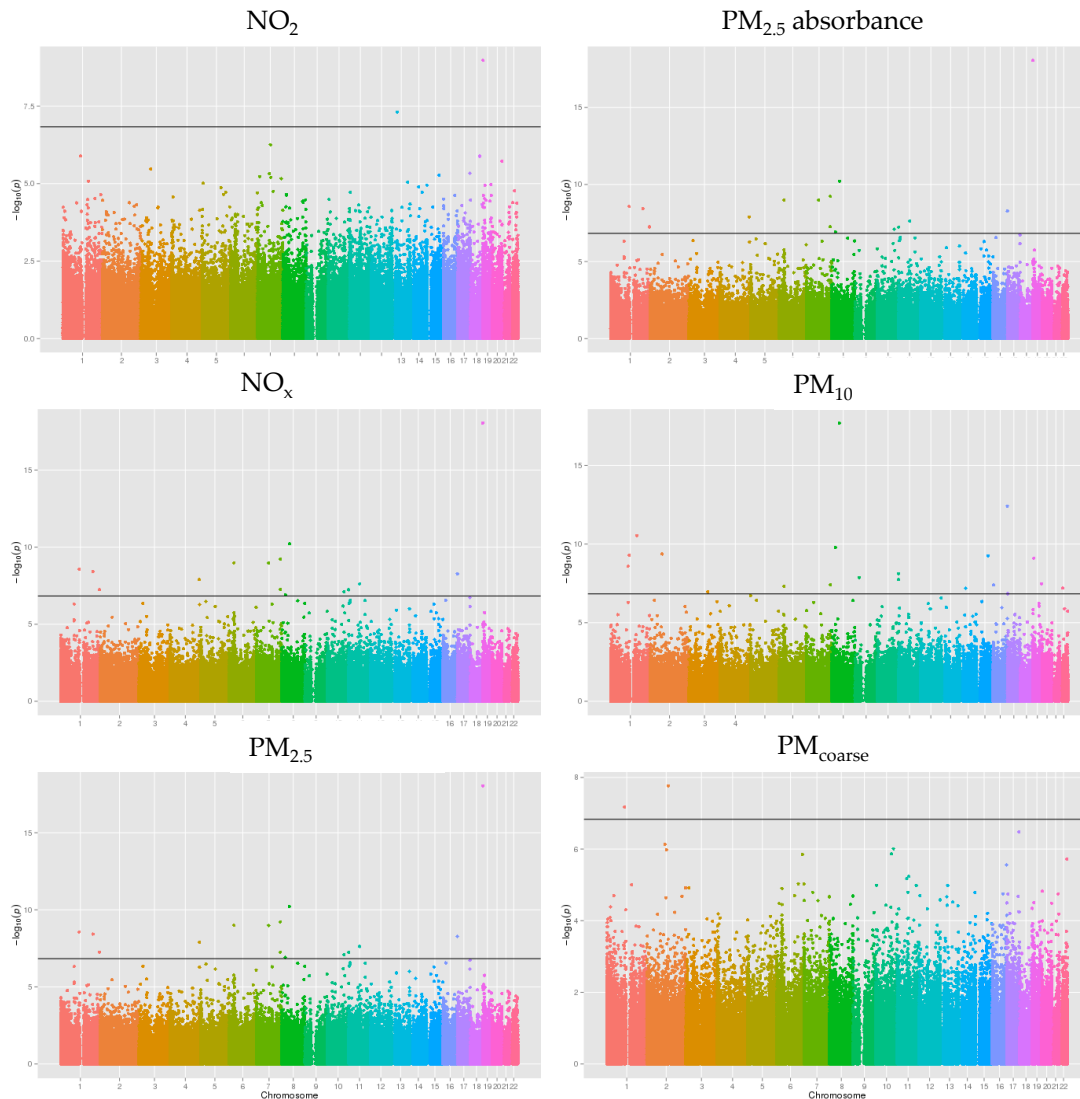


	EPIC-Italy		EPIC-NL	
	$\beta \pm \text{SE}$	p-value	$\beta \pm \text{SE}$	p-value
PM₁₀				
Somatic probes	3.43e-3 \pm 2.02e-3	0.09	8.98e-4 \pm 2.93e-4	0.79
Relation to CpG island				
Island	3.91e-4 \pm 2.05e-4	0.057	-2.22e-3 \pm 3.50e-3	0.53
Shelves	4.74e-4 \pm 4.07e-4	0.25	-1.11e-3 \pm 5.90e-3	0.85
Shores	4.62e-4 \pm 2.12e-4	0.029	1.42e-3 \pm 3.16e-3	0.65
Position on Gene				
Promoter	4.96e-4 \pm 1.77e-4	0.008	1.64e-3 \pm 3.03e-3	0.59
Gene body	3.21e-4 \pm 2.08e-4	0.17	1.94e-3 \pm 3.22e-3	0.61
Intergenic	3.97e-4 \pm 2.61e-4	0.13	-1.22e-3 \pm 3.96e-3	0.98
PM_{coarse}				
Somatic probes	5.90e-4 \pm 3.08e-4	0.06	-1.37e-3 \pm 6.74e-3	0.80
Relation to CpG island				
Island	5.36e-4 \pm 3.13e-4	0.09	-0.011 \pm 7.25e-3	0.13
Shelves	8.95e-4 \pm 6.20e-4	0.15	-3.11e-3 \pm 0.012	0.80
Shores	7.28e-4 \pm 3.23e-4	0.024	-4.43e-3 \pm 6.48e-3	0.49
Position on Gene				
Promoter	7.20e-4 \pm 2.71e-4	0.008	-2.91e-3 \pm 6.23e-3	0.64
Gene body	5.46e-4 \pm 3.17e-4	0.12	5.20e-3 \pm 6.60e-3	0.94
Intergenic	6.95e-4 \pm 3.98e-4	0.08	-3.75e-3 \pm 8.11e-3	0.64



Can we identify CpG sites whose methylation is associated with air pollution by performing an epigenome-wide association study (E_pWAS)?

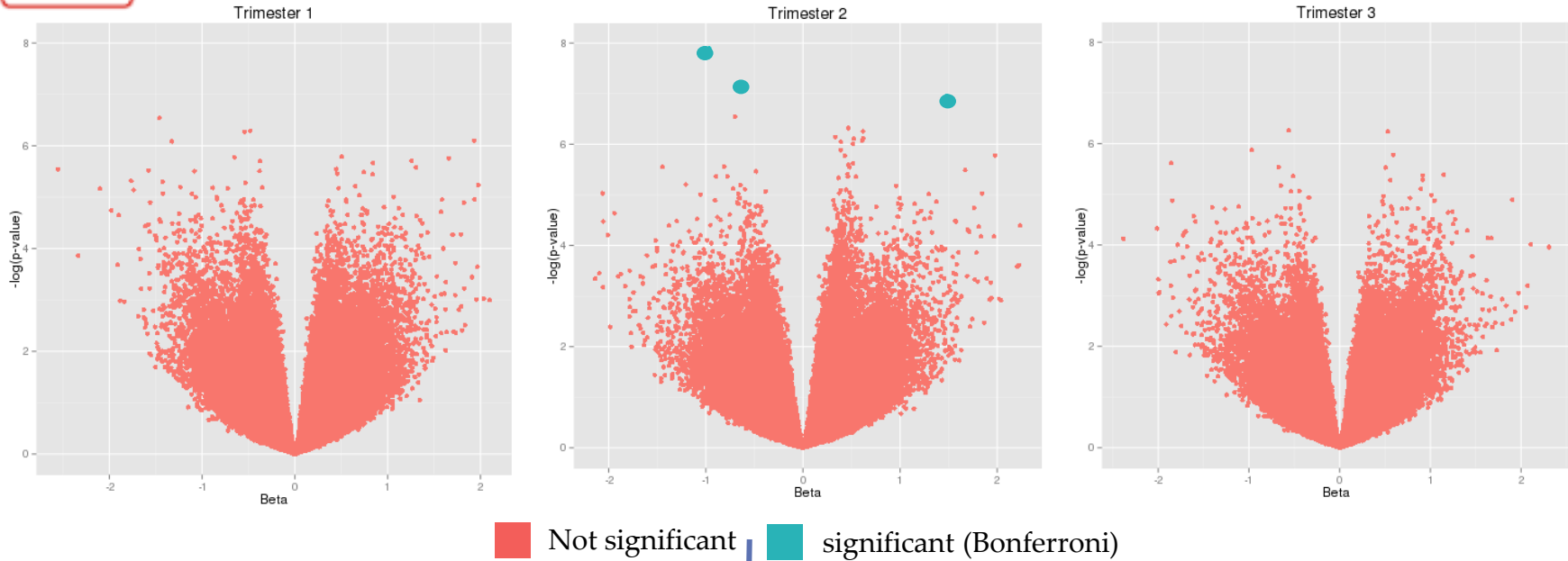
EPIC-NL



	NO_2	NO_x	$\text{PM}_{2.5}$	$\text{PM}_{2.5}^{\text{abs}}$
Hypo	10	0	1	0
Hyper	2	1	7	4
TOTAL	12	1	8	4

	NO_2	NO_x	$\text{PM}_{2.5}$	$\text{PM}_{2.5}^{\text{abs}}$	PM_{10}	$\text{PM}_{\text{coarse}}$
Hypo	2	8	17	11	4	0
Hyper	0	7	40	27	16	2
TOTAL	2	15	57	38	20	2

EpWAS in children: ALSPAC



CpG sites	Gene name	Function	Location	CGI	Beta t2	Coef t2	P-value t2
cg02669964	NA	/	NA	Island	-0,9668	0,1700	1,29E-08
cg10053355	CCDC102A	hydrolase	TSS200	Island	-0,6398	0,1188	7,24E-08
cg10537176	GPR39	Receptor / signaling	Body	NA	1,4855	0,2799	1,12E-07

- > PM₁₀ exposure during trimester 2 shows significant associations with methylation level at 3 loci on the genome.

Conclusion

This is the first epigenome- wide study on long term air pollution:

- Our data suggest that exposure to NO_x and NO_2 can lead to hypomethylation on shores and shelves.
- Probe-specific methylation changes are more unstable and not reproducible.

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EPIC study



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